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A Big Step for SIRT7, One Giant Leap for Sirtuins… in Cancer

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Recently reporting in *Nature*, Barber et al. demonstrated that SIRT7 maintains critical features that define cancer cells by removing the acetylation mark on lysine 18 of histone H3. Interestingly, hypoacetylation of H3K18 has been described as a general marker of tumor prognosis and oncoviral transformation.

Sirtuins are NAD^+-dependent deacetylases that target histone and non-histone proteins and are major factors in the response to oxidative, metabolic, and genotoxic stresses. Their responses are global and occur at many different levels; consequently, Sirtuins are at the crossroads among the foremost pathways that control cellular fate, including those for survival, genomic stability, apoptosis, and energy or metabolic adaptation. The importance of Sirtuins is reflected by their implication in several major human pathologies, including cancer, diabetes, cardiovascular diseases and neurodegenerative diseases (Bosch-Presegué and Vaquero, 2011).

Mammals have seven Sirtuins (denoted SIRT1–7) that have considerably different functions and catalytic activities. SIRT7 has been one of the most puzzling Sirtuins. Although researchers had clearly identified SIRT7 in chromatin, they had not found any clear catalytic activity or target specificity for it. The only target that had been proposed for SIRT7 was p53, but this is currently under debate. Evidence has supported a crucial role for SIRT7 in oxidative and genotoxic stress response. Homozygous knockout of *Sirt7* in mice causes diminished lifespan and leads to heart hypertrophy and inflammatory cardiopathy. Cardiomyocytes derived from these mice show increased apoptosis as well as hypersensitivity to oxidative and genotoxic stress. However, other than an ill-defined functional relationship between SIRT7 and p53 activity, no clear molecular explanation has been determined for these phenomena (Vakhrusheva et al., 2008b).

Another reported role for SIRT7 is in the control of ribosomal RNA (rRNA) expression. SIRT7 localizes mainly in the nucleolus, where it binds to the rRNA genes (rDNA) and participates in activation of RNA-polymerase I (pol-I) transcription (Figure 1A). Although this function apparently depends on SIRT7 having an intact "catalytic domain" (defined by homology to other Sirtuins), no mechanism has been described (Ford et al., 2006). However, some evidence suggests that this SIRT7 function may be specific to certain cell types (Vakhrusheva et al., 2008b; Barber et al., 2012). Interestingly, SIRT7 is relevant for the reactivation of rDNA transcription at the end of mitosis. Although the exact mechanism of SIRT7 action here is unknown, its interactions with the pol-I cofactors UBF and chromatin remodeling complex B-WICH have been described (Grob et al., 2009). Based on these findings and that SIRT7 is more abundant in highly proliferative tissues than in lowly proliferative tissues, a role for SIRT7 as a principal activator of proliferation has been proposed. On the contrary, other findings have suggested that SIRT7 may inhibit proliferation (Ford et al., 2006; Vakhrusheva et al., 2008a). This discrepancy has been a subject of controversy until now.

A recent report in *Nature* by Barber et al. (2012) represents a major breakthrough in SIRT7 research and redefines our view on the role of Sirtuins in cancer. The authors discovered a specific target of SIRT7 and identified a crucial role for SIRT7 in the maintenance of cancer phenotype and transformation. They found that SIRT7 is specific for a single histone mark, acetylated lysine 18 in histone H3 (H3K18Ac), directly linked to

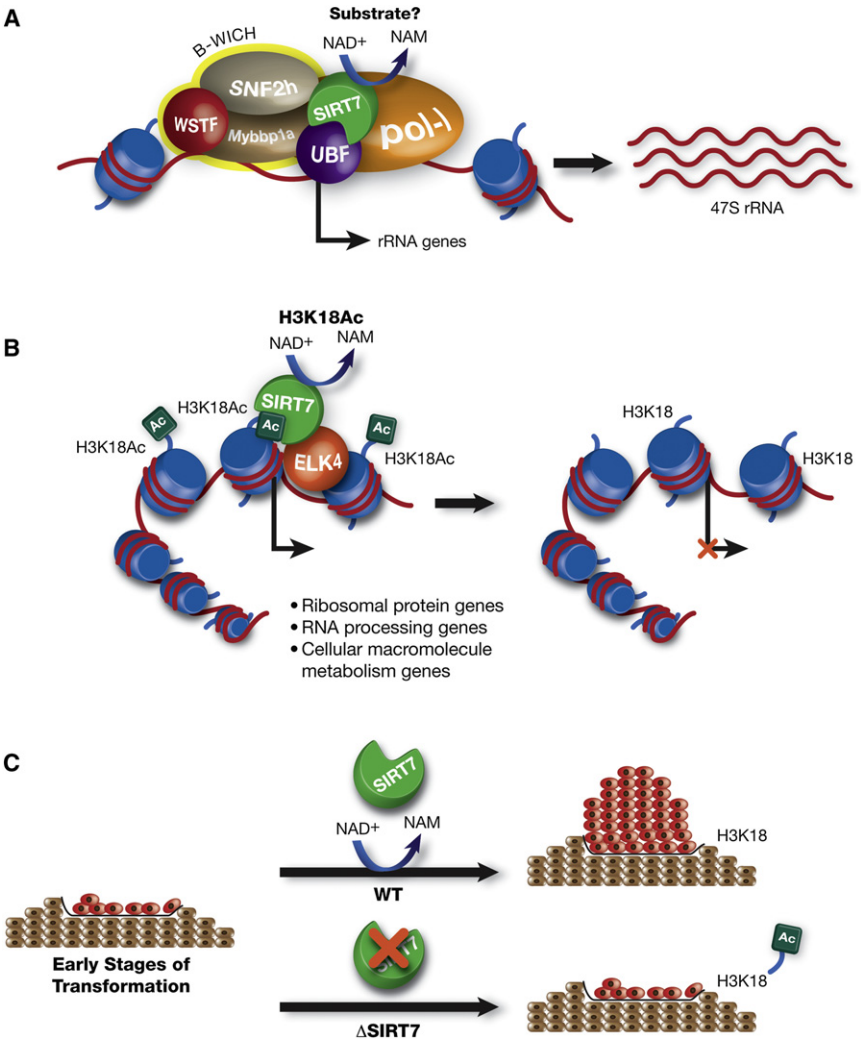

Figure 1. SIRT7 Modulates Protein Biosynthesis and Maintains Tumor Phenotype through H3K18Ac Deacetylation

(A) SIRT7 is involved in the transcription of rDNA by RNA-polymerase I (pol-I) through its catalytical activity of an undescribed substrate. For this function, SIRT7 has been shown to interact with the pol-I cofactor UBF and the UBF-binding chromatin remodeling complex B-WICH.

(B) SIRT7 represses the transcription of 241 genes, many of which are involved in protein synthesis, through deacetylation of H3K18Ac in these promoters.

(C) SIRT7 is responsible for tumor phenotype maintenance and proliferation through deacetylation of H3K18Ac. Depletion of SIRT7 inhibits tumor growth in vivo.

control of gene expression. Interestingly, H3K18Ac is mainly present in a sharp peak around the transcription start site of genes and has been linked to activation of nuclear hormone receptors (Wang et al., 2008). Moreover, H3K18 hypoacetylation has been reported as a marker of malignancy in various human cancers (Seligson et al., 2009) and has been linked to the ability of the adenovirus small early region 1a (e1a) protein to trigger oncogenic transformation (Ferrari et al., 2008; Horwitz et al., 2008).

Barber et al. (2012) performed ChIP sequencing experiments and identified 276 binding sites for SIRT7 in the genome, corresponding to 241 protein-coding genes. In 74% of these genes, SIRT7 was mainly present in the promoter proximal regions where it directly regulated the H3K18Ac level. Among the most represented genes regulated by SIRT7 through H3K18 deacetylation were those involved in different stages of regulation of protein biosynthesis, including RNA processing and protein translation (Figure 1B). Interestingly, the expression of many of these genes is deregulated in various cancers. A limitation of this study is that binding of SIRT7 to rDNA sites was not determined in this approach, as repetitive DNA sequences are not easily processed in ChIP-seq analysis. Sequence analysis of SIRT7-occupied promoters led to identification of ELK4, a MAPK-signaling dependent ETS transcription factor, as a partner of SIRT7. Almost 60% of the SIRT7-binding sites contain ELK4-binding motifs, and ELK4 depletion decreases the binding of SIRT7 at these promoters.

How this repressive regulatory function of SIRT7 in protein biosynthesis reconciles with a proactive role in rDNA transcription activation should be determined in the future; the mechanism involved in rDNA transcription is likely distinct to that of H3K18Ac deacetylation. Whether both events occur simultaneously or under different physiological conditions (e.g., stress or tumorigenesis) also remains to be addressed.

The ChIP-seq results of Barber et al. (2012) and the previously known link between H3K18Ac and cancer together corroborate an important role for SIRT7 in tumorigenesis. Consistent with this premise, SIRT7 has been reported to be upregulated in breast and thyroid cancers (Bosch-Presegué and Vaquero, 2011). Based on these findings, Barber et al. (2012) show that SIRT7 enzymatic activity is responsible for maintaining some of the most important features of human cancer cells, such as anchorage-independent growth, growth in low serum, and loss of contact inhibition. Importantly, depletion of SIRT7 inhibited the growth of human cancer cells as tumor xenografts in mice (Figure 1C). Interestingly, SIRT7 is also required for transformation by e1a and is responsible for the H3K18 hypoacetylation observed upon transformation. Given the limited number of SIRT7-regulated genes, it is possible that a small pool of genes is involved in the pro-tumorigenic function of SIRT7. In the case of e1a transformation, SIRT7 may undergo specific relocalization. Future studies should be able to clarify this issue and identify these genes.

The work of Barber et al. (2012) is a significant advance toward

understanding the implication of Sirtuins in cancer, a rather complicated subject. To date, Sirtuins have only been linked to cancer as collateral factors, rather than as direct effectors. They may help modulate various pathways that could favor or disfavor tumor development according to physiological context. Interestingly, SIRT7 is not actively involved in establishing cancer phenotype, but it is fundamental for maintaining this phenotype (Barber et al., 2012). Thus, it would be interesting to determine whether *Sirt7* knockout mice are more resistant to tumorigenesis. Whether this function stems from a specific role of SIRT7 in promoting tumor proliferation or is related to the functions of other Sirtuins, remains an open question. The relationship of this SIRT7 function to stress response and the context of this relationship are also unknown. The answer probably lies in the control of protein biosynthesis, as metabolic and energetic stress induce blockage of ribosome production and alterations in these processes are linked to tumorigenesis and aging.

In the light of the report by Barber et al. (2012), we speculate that development of specific modulators of SIRT7 may be crucial for helping control tumor progression or even for reversing cancer phenotype. Answering these questions should prove to be an exciting challenge in the future. Regardless, this work has made it clear that when it comes to cancer, Sirtuins are here to stay.

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